Adolescence Metabolic Syndrome or Adiposity and Early Adult Metabolic Syndrome

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Objective To investigate the predictive role of adolescent metabolic syndrome (MetS) in development of early adult MetS, independent of adult body mass index (BMI).

Study design 1424 adolescents (639 boys), participants of the Tehran Lipid and Glucose Study, followed for 10.4 years, were analyzed and logistic regression models were developed. Using the areas under the receiver operating characteristic curve, the discriminatory ability of adolescent MetS and overweight or obesity was evaluated. Net reclassification improvement was calculated to determine the accuracy of classification by adolescent MetS in place of overweight or obesity.

Results The mean ± SD of age and BMI were 14.6 ± 2.2 years and 20.3 ± 4.2 kg/m^2, respectively. The prevalence of MetS was 13.3% and 14.6% at baseline and after follow-up, respectively. The risk of developing early adult MetS among subjects who were overweight or obese in adolescence but nonobese as adults (OR: 1.65) was lower than the risk among subjects who were obese as adults but nonobese as adolescents (OR: 8.45). After adjustment for adult BMI, adolescent MetS and overweight or obesity did not show any association with the risk of adult MetS. Area under the receiver operating characteristic curve was higher for obesity (0.619) than MetS (0.589) and the net reclassification improvement value for MetS was 1.5% (P = .398).

Conclusion Adolescent MetS or adiposity did not predict early adult MetS independent of adult BMI. The addition of adolescent MetS to obesity does not improve the predictive power for early adult MetS. *(J Pediatr 2013;163:1663-9)*.

Metabolic syndrome (MetS) is a complex disorder defined by a cluster of interconnected factors including dyslipidemia, elevated blood pressure, and dysregulated glucose homeostasis, with abdominal obesity and/or insulin resistance as the core manifestations of the syndrome in both children and adults.[1,2] Different proposed definitions of pediatric MetS are modified from adult criteria with use of sex- and age-specific national curves; therefore, different prevalence of MetS has been reported in different studies of children and adolescents.[3]

The clinical utility of pediatric MetS for identifying who develops MetS in adulthood is controversial.[4-6] There is substantial evidence on the predictive value of childhood MetS and increased risk of MetS, type 2 diabetes, and surrogates of cardiovascular disease such as carotid intima-media thickness in adulthood.[7] To date, the contribution of childhood MetS to long-term MetS risk, independent of adult body mass index (BMI), has not been clearly established. Furthermore, some studies report that some simpler screening tools such as BMI in pediatric settings seem to be equally useful compared with pediatric MetS in identifying adolescents at risk of developing adult MetS.[7] Moreover, the majority of studies addressing role of childhood or adolescent BMI for prediction of adult MetS also failed to adjust for adult BMI.[6,8] Interestingly, the findings of 2 recent systematic reviews challenged the independent role of pediatric obesity for adult MetS and cardiovascular disease.[9,10]

Therefore, it seems important to explore predictive factors in childhood or adolescents for prediction of early adult MetS. Tracking of adiposity between childhood and adulthood would be important. In the current study, we aimed to investigate the possible role of adolescent MetS on development of early adult MetS, independent of adult BMI among the Tehran Lipid and Glucose Study (TLGS) during a mean follow-up of 10.4 years.

BMI	Body mass index
HDL-C	High-density lipoprotein cholesterol
MetS	Metabolic syndrome
NPV	Negative predictive value
NRI	Net reclassification improvement
PPV	Positive predictive value
ROC	Receiver operating characteristic
TG	Triglyceride
TLGS	Tehran Lipid and Glucose Study
WC	Waist circumference

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Methods

This study was conducted within the framework of the TLGS, a prospective study of the prevalence of noncommunicable diseases and their risk factors among Tehran's urban population.[11,12] The participants were followed up every 3 years; the baseline survey was a cross-sectional study conducted from 1999-2001, and surveys 2 (2002-2005), 3 (2006-2008), and 4 (2009-2011) were prospective follow-up surveys. Multistage cluster sampling was used to randomly select people aged 3 years or older from district 13 of Tehran, the capital of Iran. This population is served by 3 medical centers. The age distribution of the population in district 13 is representative of the overall population of Tehran (Iran National Census, 1996). Of the 15 005 subjects who participated in baseline examination of the TLGS (1999-2001), 2688 subjects were children and adolescents, aged 11-18 years (mean age 14.5 ± 2.2 years, 48% male). For the current study, after excluding those with missing anthropometric values and biochemical data (n = 106), 2582 remained. Of 2582 children and adolescents, 1424 (639 boys and 785 girls) aged 18-31 years, returned for follow-up with a mean of 10.2 years.

The protocols of this study were approved by the institutional ethics committee of the Research Institute for Endocrine Sciences, affiliated with the Shahid Beheshti University of Medical Sciences.

Anthropometric measurements including height, weight, and waist circumference (WC) were measured by trained examiners at baseline and at follow-up using standardized protocols.[11] Height was measured in a standing position, without shoes, using a measuring tape while the shoulders were in a normal position. Weight was measured using digital scales (Seca 707; Seca Corporation, Hanover, Maryland; range 0.1-150 kg) and was recorded to the nearest 100 g while the subjects were minimally clothed and without shoes. BMI (weight [kg]/square of height [m]) was calculated. WC was measured at the umbilicus, using a measuring tape without pressure to body surfaces and was recorded to the nearest 0.5 cm. Systolic and diastolic blood pressure was measured using a standard mercury sphygmomanometer (calibrated by the Iranian Institute of Standards and Industrial Researches), in the right arm after 15-minute rest in a sitting position. A qualified physician measured the blood pressure of the seated subject twice; the mean of the 2 measurements was used in the analysis. A blood sample was drawn into vacutainer tubes from all subjects between 7:00 a.m. and 9:00 a.m. after 12-14 hours overnight fasting for measurement of glucose and lipid concentrations. The samples were centrifuged 30-45 minutes after collection. All analyses were done at the TLGS research laboratory on the day of blood collection. Fasting plasma glucose was measured by the enzymatic colorimetric method using glucose oxidase. Serum triglyceride (TG) was assayed using an enzymatic colorimetric method with glycerol phosphate oxidase, and serum total cholesterol was assayed using an enzymatic colorimetric method with cholesterol esterase and cholesterol oxidase. High-density lipoprotein cholesterol (HDL-C) was measured after precipitation of the apolipoprotein B–containing lipoproteins with phosphotungstic acid. These analyses were performed using commercial kits (Pars Azmoon Inc, Tehran, Iran) and a Selectra 2 auto analyzer (Vital Scientific, Spankeren, The Netherlands). Inter- and intra-assay coefficients of variations at baseline were 2.2% for serum glucose, 2% and 0.5% for HDL-C, and 1.6% and 0.6% for TG, respectively.

Because no universally accepted definition of the MetS exists for children, the definition proposed by Cook et al was used.[13] It defines MetS as 3 or more of the following: fasting TGs ≥110 mg/dL; HDL-C <40 mg/dL; WC ≥90th percentile for age and sex, according to national reference curves[14]; systolic blood pressure and/or diastolic blood pressure ≥90th percentile for sex, age, and height, from the National Heart, Lung, and Blood Institute's recommended cut-off points;[15] and fasting blood glucose ≥100 mg/dL, according to the recent recommendations of American Diabetes Association.[16] The joint interim statement[17] defines MetS as the presence of any 3 of 5 risk factors of the following: (1) abdominal obesity as WC ≥91 cm for women and ≥89 cm for men according to population- and country-specific cut-off point for Iranians[18]; (2) fasting plasma glucose ≥100 mg/dL or drug treatment; (3) fasting TGs ≥150 mg/dL or drug treatment; (4) fasting HDL-C <50 mg/dL for women and <40 mg/dL for men or drug treatment; and (5) elevated blood pressure was defined as systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, or antihypertensive drug treatment.

Obesity, overweight, and normal BMI were defined based on the standardized percentile curves of BMI suggested for Iranian children and adolescents as ≥95th, between ≥85th and <95th, and <85th percentiles of BMI for age and sex, respectively.[19] To observe tracking of BMI from adolescence into early adulthood, the participants were categorized into 4 groups on the basis of adiposity status in adolescence and adulthood. Group I were defined as subjects with normal BMI in adolescence who were nonobese as adults; group II, those who were overweight or obese in adolescence but nonobese as adults; group III, those with normal BMI in adolescence who were obese as adults; and group IV, those who were overweight or obese in adolescence and obese as adults.

Statistical Analyses

Baseline and follow-up characteristics of subjects were expressed as mean and SD or median and IQR for continuous variables and percentages for dichotomous variables. These variables were compared among adiposity groups using the one-way ANOVA for continuous variables and χ^2 test for categorical variables. The variables without normal distribution were log transformed. Multiple logistic regression analysis was used to evaluate the predictive power of adolescent MetS, overweight or obesity, and abdominal obesity for adult MetS. ORs and 95% CIs were calculated for boys and girls. Furthermore, the predictive power of adiposity groups for

adult MetS was reported. Areas under the receiver operating characteristic (ROC) curve were estimated to compare the prediction power of adolescent MetS, overweight or obesity, and abdominal obesity for adult MetS. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. The increased discriminative value of adding adolescent MetS and abdominal obesity to adolescent overweight or obesity model was further tested with net reclassification improvement (NRI). NRI examined how many individuals changed the status of adolescent overweight or obesity after addition of adolescent MetS or abdominal obesity reporting the proportion of individuals correctly reclassified across risk categories minus the proportion of individuals incorrectly reclassified. The percentiles of systolic and diastolic blood pressure were calculated according to the fourth report on the diagnosis, evaluation, and treatment of high blood pressure.[20]

The mean follow-up time was 10.4 years. Data analyses were carried out by SPSS software package (v. 15; SPSS Inc, Chicago, Illinois) and SAS software (v. 9.1; SAS Institute, Cary, North Carolina) The statistical significance of differences between ROC curves was assessed using STATA software package v. 10.0 (Stata Corporation, College Station, Texas) according to the algorithm developed by Delong et al[21] and significance was set at $P < .05$.

Results

The study cohort consisted of 1424 subjects (639 boys and 785 girls) with a mean (±SD) age of 14.6 ± 2.2 years at baseline. The mean length of follow-up was 10.4 ± 1.0 years. There were no significant differences in mean baseline anthropometric measurements and biochemical assessments between the subgroups of the cohort that provided follow-up assessments and those lost at baseline (**Table I**; available at www.jpeds.com).

Among 1121 subjects who had had normal weight as children, 60 (5.3%) were obese as adults. Among 303 subjects who had been obese as children, 141 (46.5%) were obese as adults. The prevalence of abdominal obesity, MetS, and overweight or obesity among children were 15.3% (15.5% of boys and 15.1% of girls), 13.3% (14.4% of boys and 12.4% of girls), and 21.3% (23.3% of boys and 19.6% of girls), respectively. After a 10-year follow-up, the prevalence of MetS was 14.6% (29.7% and 2.4% for adult males and females, respectively). Adolescence and early adult characteristics of the participants according to adiposity groups are displayed in **Table II**. Compared with subjects in group I, those in group IV had unfavorable cardiometabolic characteristics, both during adolescence and adulthood ($P < .05$). Adolescents in group II had higher adolescent weight, BMI, WC, and TGs compared with those in group III ($P < .05$). The prevalence of adolescent MetS was higher in group II in comparison with group III (38.3% vs 11.7%, $P < .05$); however, the prevalence of early adult MetS was higher in group III in comparison with group II (45.0% vs 13.0%, $P < .05$).

The risk of developing early adult MetS among subjects who were overweight or obese in adolescence but nonobese as adults (group II) was not significantly increased compared with subjects who had normal BMI in adolescence but nonobese as adults (group I). Subjects who were obese as adults, irrespective of their adolescent adiposity status (groups III and IV) had increased risks of developing early adult MetS (**Table III**).

The risk of early adult MetS tended to increase as the number of youth MetS components increased (P for trend <.001). However, after adjustment for adult BMI, all associations were not significant, except for boys who had 2 (2.52, 95% CI: 1.37-4.64) or 3 (2.35, 95% CI: 1.12-4.93) MetS components. The most frequent combination of unfavorable cardiometabolic risk factors for boys with 2 or 3 MetS components were low HDL-C and high TGs. Adolescent MetS, overweight or obese, and abdominal obesity had independent associations with early adult MetS. However, after adjustment of adult BMI, all associations were not significant, except for adolescent abdominal obesity in boys (0.57, 95% CI: 0.33-0.96), which was protective (**Table IV**).

All predictors had high NPV, indicating that normal BMI or WC and lack of MetS in adolescence can accurately predict lack of MetS in early adulthood. Also, all predictors had low PPV, indicating that majority of adolescents with overweight obesity, abdominal obesity, and MetS do not necessarily develop MetS in early adulthood. Prediction of early adult MetS by adolescent overweight or obesity using ROC analysis was superior to the prediction provided by adolescent abdominal obesity ($P = .003$). Additionally, compared with adolescent MetS, borderline significance ($P = .07$) was observed. As evidenced by net reclassification index values, the accuracy of classification was not improved by adding either adolescent MetS or abdominal obesity to adolescent overweight or obesity for prediction of early adult MetS (all $P > .05$, **Table V**).

Discussion

This study demonstrates the predictive power of adolescence MetS or obesity for early adult MetS and the tracking of adiposity between adolescence and adulthood for adult MetS prediction. We found that adolescent MetS or excess weight did not predict early adult MetS, independent of adult BMI during a mean follow-up of 10.4 years. Also, the risk of developing MetS in early adulthood was lower among subjects who were overweight or obese during adolescence but nonobese as adults than among subjects who were consistently obese or who became obese as adults. Furthermore, our analysis revealed no marked change for the future MetS stratification by adolescent MetS beyond adolescent obesity.

MetS is a subject of controversy in adolescence, which raises questions about the utility of the MetS as a diagnostic category in a clinical setting. Barriers of using MetS are the lack of consistent, accepted definition, the physiological occurrence of insulin resistance in puberty, and the low stability of the MetS in children and adolescents.[2,22] Moreover, there is not enough evidence in favor of the independent role

Table II. Participant characteristics during adolescence and adulthood according to adiposity groups

	Group I: BMI <85th at adolescence and <30 kg/m² at adulthood (n = 1061)	Group II: BMI ≥85th at adolescence and <30 kg/m² at adulthood (n = 162)	Group III: BMI <85th at adolescence and ≥30 kg/m² at adulthood (n = 60)	Group IV: BMI ≥ 85th at adolescence and ≥30 kg/m² at adulthood (n = 141)	*P* value*
Adolescence					
Age (y)	14.4 ± 2.2‡,§	14.4 ± 2.2§	15.5 ± 2.1	14.9 ± 2.2§	.001
Male (%)	42.9	43.2	58.3	56.0	.004
Family history of diabetes (%)	9.6	12.4	15.0	17.3	.029
BMI (kg/m²)	18.5 ± 2.4‡,§,¶	25.4 ± 2.7§,¶	21.2 ± 3.4¶	27.5 ± 3.9	<.001
WC (cm)	65.5 ± 7.0‡,§,¶	80.3 ± 8.4§,¶	72.8 ± 6.3¶	85.9 ± 10.4	<.001
Abdominal obesity (%)	3.3	50.3	8.5	68.1	< .001
Systolic blood pressure (mm Hg)	102.9 ± 10.8‡,§,¶	110.4 ± 10.5¶	108.4 ± 9.9¶	114.4 ± 12.6	<.001
Percentile	31.1 ± 24.7‡,¶	48.8 ± 26.5§	35.2 ± 25.7¶	55.0 ± 28.7	<.001
Diastolic blood pressure (mm Hg)	69.6 ± 9.0‡,¶	74.1 ± 7.9¶	72.3 ± 7.3¶	75.5 ± 9.4	<.001
Percentile	65.6 ± 26.4‡,¶	78.0 ± 21.7	69.7 ± 22.8	79.1 ± 23.8	<.001
Elevated blood pressure (%)	13.9	30.0	21.7	38.1	<.001
HDL-C (mg/dL)	43.6 ± 10.3¶	41.4 ± 10.6	42.3 ± 11.0	39.8 ± 8.5	<.001
TGs (mg/dL)†	94.0 (71.0-126.0)‡,¶	120 (88.0-162.2)§	94.0 (69.0-131.0)¶	133.0 (93.5-188.5)	<.001
Fasting plasma glucose (mg/dL)	88.2 ± 8.0‡	90.6 ± 7.9¶	87.6 ± 8.8	87.9 ± 7.7	.004
MetS (%)	5.2	38.3	11.7	46.1	<.001
Early adulthood					
Age (y)	24.9 ± 2.5§,¶	24.9 ± 2.4§	26.2 ± 2.3	25.5 ± 2.6	<.001
BMI (kg/m²)	23.2 ± 3.1‡,§,¶	26.5 ± 3.1§,¶	32.5 ± 2.6¶	34.5 ± 3.9	<.001
WC (cm)	81.6 ± 9.2‡,§,¶	89.0 ± 9.2§,¶	103.2 ± 8.4	106.1 ± 12.7	<.001
Abdominal obesity (%)	21.7	45.1	93.3	91.5	<.001
Systolic blood pressure (mm Hg)	105.0 ± 11.7§,¶	107.6 ± 11.8§,¶	116.1 ± 12.2	118.6 ± 13.3	<.001
Diastolic blood pressure (mm Hg)	70.2 ± 9.0§,¶	71.5 ± 9.0§,¶	79.7 ± 9.6	78.6 ± 10.7	<.001
Elevated blood pressure (%)	1.8	3.1	18.3	18.7	<.001
HDL-C (mg/dL)	49.7 ± 11.6§,¶	49.6 ± 11.7§,¶	41.7 ± 8.6	43.2 ± 9.6	<.001
TGs (mg/dL)†	84.0 (64.5-115.0)§,¶	82.0 (64.7-117.2)§,¶	127.0 (103.0-172.5)	123.0 (90.0-169.5)	<.001
Fasting plasma glucose (mg/dL)	88.9 ± 15.2	89.1 ± 7.7	90.4 ± 6.3	91.9 ± 15.7	.106
MetS (%)	9.0	13.0	45.0	46.8	<.001

Data are mean ± SD or median (IQ 25-75) unless otherwise noted.
**P* values are for the comparisons across groups, with the use of ANOVA for continuous and χ^2 test for categorical variables.
†Log transformed values were used for comparison.
‡Significantly different from group II, using post hoc Scheffe analysis test.
§Significantly different from group III, using post hoc Scheffe analysis test.
¶Significantly different from group IV, using post hoc Scheffe analysis test.

of adolescent MetS for future MetS prediction. For example, the Bogalusa Heart Study did not consider the adult BMI in evaluating the association between adolescent and adult MetS.[7] Similarly, our unadjusted analysis indicated an association between adolescent MetS and early adult MetS; however, after adjusting the adult BMI, no association was observed except for some combinations of cardiometabolic risk factors.

Interestingly, combinations of 2 or 3 elements of MetS remained significant after adjustment for adult BMI. Further analysis revealed that combination of low HDL-C and high TGs or the combination of low HDL-C, high TGs, and

Table III. ORs and 95% CI of developing early adulthood MetS in adiposity groups

	Boys		Girls		Total	
	OR* (95% CI)	*P* value	OR* (95% CI)	*P* value	OR† (95% CI)	*P* value
Group I: BMI <85th at adolescence and <30 kg/m² at adulthood (n = 1061)	1.00		1.00			
Group II: BMI ≥85th at adolescence and <30 kg/m² at adulthood (n = 162)	1.62 (0.92-2.86)	.095	1.32 (0.15-11.43)	.800	1.59 (0.92-2.74)	.094
Group III: BMI <85th at adolescence and ≥30 kg/m² at adulthood (n = 60)	8.45 (4.18-18.73)	<.001	16.39 (3.68-72.96)	<.001	9.66 (4.93-18.91)	<.001
Group IV: BMI ≥ 85th at adolescence and ≥30 kg/m² at adulthood (n = 141)	9.87 (5.77-16.90)	<.001	23.11 (7.62-70.16)	<.001	11.82 (7.27-19.23)	<.001
P for trend	<.001		<.001		<.001	

*Unadjusted.
†Adjusted for sex.

Table IV. OR (95% CI) of developing MetS in early adulthood based on metabolic and obesity characteristics in 639 boys and 785 girls

	Boys (n = 639)		Girls (n = 785)		Total (n = 1424)		
	Unadjusted	Adjusted for adult BMI	Unadjusted	Adjusted for adult BMI	Unadjusted	Adjusted for sex	Adjusted for sex and adult BMI
No. of MetS components							
0	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1	1.74 (1.05-2.89) .03	1.35 (0.77-2.38) .29	3.05 (0.63-14.83) .17	4.02 (0.70-23.2) .12	1.88 (1.19-2.98) .007	1.85 (1.14-3.00) .012	1.54 (0.91-2.62) .11
2	3.85 (2.25-6.58) <.001	2.52 (1.37-4.64) .003	2.13 (0.39-11.77) .38	1.58 (0.24-10.21) .63	2.60 (1.62-4.17) <.001	3.55 (2.14-5.89) <.001	2.33 (1.32-4.11) .003
3	7.26 (3.90-13.54) <.001	2.35 (1.12-4.93) .024	6.19 (1.11-34.52) .037	2.93 (0.44-19.28) .26	5.52 (3.29-9.26) <.001	7.05 (3.95-12.56) <.001	2.44 (1.25-4.76) .009
≥4	7.88 (3.18-19.56) <.001	0.43 (0.13-1.41) .16	11.74 (1.56-88.05) .017	2.84 (0.28-28.46) .38	7.13 (3.48-14.62) <.001	8.58 (3.73-19.76) <.001	0.67 (0.23-1.95) .48
P for trend	<.001	.069	<.001	.57	<.001	<.001	.047
Adolescence MetS	3.96 (2.53-6.21) <.001	1.08 (0.61-1.93) .78	3.49 (1.29-9.41) .014	1.39 (0.45-4.26) .56	3.32 (2.34-4.71) <.001	3.88 (2.58-5.83) <.001	1.16 (0.70-1.94) .56
Adolescence abdominal obesity	3.17 (2.05-4.89) <.001	0.47 (0.26-0.85) .013	4.41 (1.74-11.21) .002	1.00 (0.33-3.05) .996	2.74 (1.95-3.86) <.001	3.36 (2.26-4.98) <.001	0.57 (0.33-0.96) .035
Adolescence overweight or obese	3.40 (2.32-4-98) <.001	0.60 (0.35-1.01) .056	6.01 (2.38-15.21) <.001	0.98 (0.30-3.20) .98	3.30 (2.42-4.50) <.001	3.70 (2.60-5.26) <.001	0.67 (0.41-1.07) .096

Abdominal obesity was defined as WC ≥90th national percentile.
Overweight or obesity was defined as BMI ≥85th national percentile.

abdominal obesity are the more prevalent patterns. These findings are in agreement with a previous cross-sectional report from the TLGS, suggesting the hypertriglyceridemic waist phenotype as a simple marker of identifying adolescents at risk of MetS and other metabolic abnormalities.[23] More importantly, these findings indicate that some combinations of individual components included in the definitions of the adolescent MetS would be more predictive than the whole syndrome and could provide evidence in favor of unequal weight of different components. Unexpectedly, abdominal obesity remained as a protective variable in the final model (0.57, 95% CI: 0.33-0.96). One explanation behind this observation is the high occurrence of normal adult BMI (53%) in those adolescents with abdominal obesity, which probably reversed the expected association of abdominal obesity.

Giving the importance of tracking BMI from adolescence to adulthood and similar to the findings of Juonala et al,[24] we found that subjects, who had normal BMI in adolescence

Table V. Sensitivity, specificity, PPV, NPV, AUC, and NRI values for adolescence MetS, overweight or obesity, and abdominal obesity in predicting early adulthood MetS

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	95% CI	NRI (%)	*P* value
Total								
Overweight or obesity	42	82	29	89	0.619*,†	0.576-0.663	-	-
MetS	28	89	31	88	0.589	0.544-0.633	1.51%	.398
Abdominal obesity	29	87	28	88	0.580	0.536-0.624	<0.1%	.399
Boys								
Overweight or obesity	40	84	51	77	0.618‡	0.569-0.668	-	-
MetS	28	91	57	75	0.596	0.545-.646	3.05%	.397
Abdominal obesity	52	75	28	89	0.584	0.534-0.634	<0.1%	.399
Girls								
Overweight or obesity	58	81	7	99	0.696	0.564-0.829	-	-
MetS	32	88	6	98	0.599	0.457-0.742	<0.1%	.399
Abdominal obesity	42	86	7	98	0.640	0.498-0.781	<0.1%	.399

AUC, area under the curve.
*P =.07 in comparison to MetS using χ^2 test.
†P = .003 in comparison to abdominal obesity using χ^2 test.
‡P = .02 in comparison to abdominal obesity using χ^2 test.

but who became obese as adults, had risk of adult MetS similar to those who were consistently obese; however, those who were overweight or obese as children but who became nonobese as adults had a MetS risk that was similar to that of persons who were never obese. From the practical point of view, in spite of lack of knowledge of adult BMI and based on the current analysis, when we are faced with overweight or obese children, we can advise them to get to an appropriate BMI in the future to prevent MetS in adult years. Moreover, we found low PPV and high NPV of adolescent obesity and MetS for early adult MetS, indicating that adolescent obesity or MetS could be a useful screening tool for identifying adolescents who are not at risk for development of adult MetS. In spite of nonsignificant values, using ROC analysis, it seems that adolescent obesity had higher area under curve compared with MetS, challenging the clinical utility of accepted pediatrics MetS definition. However, obesity in adolescence had a higher area under curve compared with abdominal obesity. The area under the curve values were lower than 0.7, meaning that the prediction can be interpreted as fair.

Using sophisticated analysis, NRI showed nonsignificant values for adolescent MetS, suggesting that adding adolescent MetS to a model with adolescent obesity does not increase the predictive ability of obesity for early adult MetS. Our findings in terms of NRI are in line with the Bogalusa Heart Study,[7] which did not show any superiority for adolescent MetS in comparison with those of adolescent obesity by high BMI.

The findings in this report are subject to some limitations. First, the present study had high rate of loss to follow-up. However, there were no significant differences between subjects lost to follow-up and those provided follow-up assessments. Furthermore, some possible confounders such as physical activity, dietary habits, and socioeconomic status were not taken into account. Given the low incidence of MetS in girls, this study was not adequately powered for sex-stratified subgroup analysis. Finally, the stage of puberty was not considered in our analysis. There are strengths of the current survey. There was a relatively large sample size. We also used national cut points for defining MetS in adolescence and adulthood.

Considering the complexity surrounding the various definitions of adolescent MetS, our results potentially propose independent roles for some combinations of risk factors especially the hypertriglyceridemic waist. However, the clinical utility of these combinations should be further analyzed in long-term cohort studies. ■

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50 Years Ago in *The Journal of Pediatrics*

Autoimmune Disorders of Endocrine Glands

Solomon IL, Blizzard RM. J Pediatr 1963;63:1021-33

In their insightful article, Solomon and Blizzard reviewed data that substantiated Witebsky's postulates pointing to autoimmunity in 3 endocrine diseases: Hashimoto's thyroiditis, Addison's disease, and male infertility. They correctly hypothesized that additional 'idiopathic' endocrine disorders would have a similar autoimmune etiology including diabetes, hypoparathyroidism, panhypopituitarism, and ovarian failure.

These investigators implicated a disturbance in immune tolerance, but precise mechanisms were lacking. The role and identity of environmental triggers in a genetically susceptible individual, as well as the indolent nature of autoimmunity prior to overt disease were not discussed.[1]

We have discovered many molecular and cellular entities required to establish and maintain central and peripheral self-tolerance. T-cell subsets are the key mediators in autoimmune thyroiditis and adrenal failure and type 1 diabetes. B-cell subsets contribute to autoimmunity through antigen presentation, cytokine synthesis, and auto-antibody production. Many target antigens have been identified; antibodies to these help us predict, diagnose, and follow disease activity.[2]

In this genetic era, monogenic causes of autoimmunity have produced insight into pathways to tolerance (for example *AIRE*: genetic defects cause autoimmune polyendocrinopathy candidiasis and ectodermal dystrophy/autoimmune polyglandular syndrome-1). Genome-wide association studies and observations of phenotypic variability among individuals with the same mutations have lead to appreciation of the role of multiple protective and susceptibility loci, both within and beyond the major histocompatibility complex locus. Discovery of epigenetic control of many immune cell functions raises additional questions about the role of DNA methylation, histone modifications, and noncoding microRNA in the development of tolerance to self.[3]

Drugs and biologics to treat/delay onset of more serious autoimmune endocrinopathies have emerged including nonselective antiproliferative agents, agents that selectively block cytokine-mediated lymphocyte stimulation, T- and B-cell depletion with monoclonal antibodies and peptide antagonists, and fusion proteins that target kinases.[3,4] In short, we have come a long way, but it behoves us to remember those who set the stage.

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Table I. Comparison of baseline characteristics between subjects followed-up and missed to follow-up

	Follow-up (n = 1424)	Missed to follow-up (n = 1264)	*P* value
Age (y)	14.5 ± 2.2	14.5 ± 2.3	.163
Weight (kg)	51.4 ± 14.4	51.3 ± 15.0	.159
Height (cm)	158.0 ± 11.3	158.0 ± 11.7	.108
BMI (kg/m^2)	20.3 ± 4.2	20.2 ± 4.3	.223
WC (cm)	69.5 ± 10.5	69.7 ± 10.8	.211
Fasting blood glucose (mg/dL)	88.4 ± 8.0	89.0 ± 12.5	.578
HDL-C (mg/dL)	42.9 ± 10.3	42.9 ± 10.2	.849
TGs (mg/dL)	112.7 ± 57.8	109.2 ± 65.3	.603
Systolic blood pressure (mm Hg)	105.1 ± 11.6	105.5 ± 12.2	.030
Diastolic blood pressure (mm Hg)	70.8 ± 9.1	71.3 ± 9.3	.808